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DYNAMIQUE MOLECULAIRE DES
INTERACTIONS MEMBRANAIRES.
URA CNRS 1856

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NIH-R1 Final Report :

Procedures proposed for the NIH-R1 experiment entitled :

*"Maturation of cardiac and hypothalamic natriuretic peptide system
in rat fetuses developing under reduced gravity conditions,
with a special attention given to the fine structure, protein and ANP-receptor expression
in fetal and neonatal choroid plexus",*

were performed during and after the mission as expected. Hearts and brains from fetuses, pups and dams flown on STS 66 and their ground controls were dissected and postflight operations were made as exposed in ERD and HIRD. Electron microscopy and immunocytochemistry studies were achieved at the end of 1995. PCR and in-situ hybridization procedures are still in progress. At this moment, first scientific conclusions have been obtained and are summarized in this report.

Results have been obtained on the effects of spaceflight (11-day flight, from day 9 to day 20 of the gestation) on the maturation of choroid plexus (CPX) and formation of cerebral ventricles, in fetuses and new-born rats, on the choroidal response of dams, after return to earth and, partially, on the natriuretic peptide system (NPS) in heart and hypothalamus.

1) CHOROID PLEXUS DURING DEVELOPMENT.

Choroidal cells early differentiate and secrete cerebrospinal fluid (CSF) in cerebral cavities, which are larger in fetuses than in adults. Consequently, it is admitted that CPX plays an important role in fetal growth and development of the brain. After an 11-day spaceflight, no clear changes were noticed in the fine structure of apical microvilli in fetal or new-born choroidal cells when observed by electron microscopy. However, immunodetection of structural and/or functional markers demonstrated that a development in reduced gravity alters the choroidal cell differentiation. Indeed, the distribution of ezrin, (an actin- and membrane-associated protein, involved in the structural formation and maintenance of apical microvilli, in choroid plexus) and aquaporin CHIP 28 (CHannel Integral Protein, 28 kDa, a water channel which is a major protein of the apical membrane domain in choroidal cells), showed that, despite the normal structure of microvilli in CPX cells (observed with electron microscopy), the molecular differentiation of the CPX apical domain is delayed in fetuses, after a spaceflight, as shown by the cytosolic presence of ezrin in CPX of "Flight" animals and by the decreased immunoreaction to anti-CHIP 28 antibodies.

Conversely, carbonic anhydrase II (CA II, an enzyme involved in the CSF production) was obviously increased in CPX of fetuses developed aboard the shuttle. This could reflect an increased CA II-dependent production of CSF in fetuses after a spaceflight. We observed, using the OPTILAB® program for image analysis, that ventricular

volumes of fetuses developing for 11 days in space are significantly increased (+30%) when compared with those of synchronous control fetuses.

These data suggest that choroid plexus of rats developing in space, demonstrated a delayed maturation characterized by the reduced distribution of apical markers and the possibly increased CSF production in fetuses, displayed by the increased distribution of CA II and by the enlarged ventricular volumes.

2) CHOROID PLEXUS IN ADULT RATS AFTER A SPACEFLIGHT.

During previous experiments on weightlessness effects (SLS-2 experiments), CPX from male adult rats dissected inflight demonstrated a partial loss of microvilli and cell polarity, with a clear increase in intracytoplasmic vesicles, what led us to hypothesize that microgravity induces a reduced CSF production in adults (Gabrion et al, 1995). NIH-R1 experiments allowed us to further investigate this point : after 11 days in space and 2 days of 1-G readaptation, important alterations were noticed in the fine structure of apical microvilli in dam choroidal cells when observed by electron microscopy. Two days after landing, choroidal microvilli were very high and large, what is in agreement with the intense restoration of choroidal CSF production of Flight dams.

3) CARDIAC AND HYPOTHALAMIC NPS DURING DEVELOPMENT.

First data obtained by Davet et al. (1995) showed that a spaceflight does not modify the onset of NPS (natriuretic peptide system) : ANP (atrial natriuretic peptide) storage in cardiac atria of fetuses developed in flight is very similar to levels observed in synchronous controls. No changes were observed by immunocytochemistry and electron microscopy, in the maturation of hypothalamic NPS in flight fetal and newborn rats. We conclude that development in space does not alter the onset of the endocrine function of heart and the production of NP in the fetal brain.

4) CARDIAC AND HYPOTHALAMIC NPS OF DAMS AFTER SPACEFLIGHT.

No changes have been observed in the fine structure and anti-ANP immunoreactivity of flight dam atria, 2 days after return from an 11-day spaceflight. First results obtained with RT-PCR analyses confirmed the absence of modifications in the ANP biosynthesis and storage of flight dam left atria. Conversely, BNP (brain natriuretic peptide) storage is clearly increased in hypothalamus of "Flight" dams, at the level of the supraoptic nuclei, two days after landing.

CONCLUSION.

The reversible effects of an 11-day spaceflight on the maturation of choroid plexus and the absence of alterations on the natriuretic peptide system in heart and hypothalamus have been evidenced with studies performed on fetuses and pups developed in space. Effects on dams choroid plexus, hypothalamus and heart are in accordance with the data previously obtained with the SLS-2 experiments.

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